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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/645,321	08/25/2000	SATOSHI KOIZUMI	5.1183	3262

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EXAMINER

RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
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1652

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DATE MAILED: 03/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/645,321

Applicant(s)

KOIZUMI ET AL.

Examiner

Manjunath N. Rao, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2, 11.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

The request filed on 12-2-02 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/645,321 is acceptable and a RCE has been established. An action on the RCE follows.

Claims 4-22 are currently pending in this application. Applicants' amendments filed on 12-2-02, paper No.10 and that filed on 1-9-03, paper No.12, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/645,321, filed on 8-25-00. However, the priority document is in Japanese and therefore Examiner has not granted the priority date. Priority will be granted upon submission of an English translation of the priority document.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 6-16, 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 4, 6-16, 19-22 recite the phrase “derived from a microorganism belonging to genus *Synechocystis*...”. The metes and bounds of this phrase is not clear to the Examiner. Literally, while the term “derive” means “to isolate from or obtain from a source”, the above term could also mean “to arrive at by reasoning i.e., to deduce or infer” or also as “to produce or obtain from another substance”. Therefore, it is not clear to the Examiner either from the specification or from the claims as to what applicants mean by the above phrase. It is not clear to the Examiner whether the above “derived epimerase” encompasses a single specific epimerase of a *Synechocystis* as in “isolated from a specific *Synechocystis* species and strain” or whether it encompasses recombinants, variants and mutants of any epimerase obtained from any source or modified epimerases from any other source and labeled as “derived from *Synechocystis*”. As applicants have not provided a definition for the above phrase, Examiner has interpreted the claims broadly to mean, that a the above phrase encompasses epimerases which are recombinants, variants, or mutants of any epimerase from any source. Examiner has given the same interpretation while considering the claims for all other rejections.

Claims 4-5, 17-20 and claims 6-16, and 21-22 which depend from claims 4-5 and /or 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

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particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 4-5, 17-20 recite the phrase "treated matter of the culture". It is not clear to the Examiner as to what applicants mean by the above phrase. The metes and bounds of the above phrase especially in the context of the different treatments of the culture matter is not clear to the Examiner. A perusal of the above specification does not provide a specific definition for the above phrase either, thus rendering the claims indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 6-16, 19-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 4, 6-16, 19-22 are directed to a method of making sialic acid using epimerase derived from *Synechocystis* microorganism. Claims 4, 6-16, 19-22 are rejected under this section of 35 USC 112 because the claims are directed to a method wherein a genus of polypeptides derived from SEQ ID NO:1 including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:1 and fragments of SEQ ID NO:1 is used but have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:1 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of either the structure of all the polypeptide

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sequences derived from SEQ ID NO:2, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed for use in the method is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 4, 6-16, 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vann(a) et al. (Glycobiology, 1997, Vol. 7(5):697-701), or Vann(b) et al. (J. Biol. Chem., 1987, Vol. 262(36):17556-62), and Maru et al. (Carbohydrate Research Vol. 306:575-578). Claims 4, 6-16, 19-22 are drawn to a process of producing N-acetylneuraminic acid (NANA) which comprises allowing either individually (as in claims 17-20) or a combination (as in claim 4) of a culture of a microorganism having NANA aldolase activity or NANA synthetase activity or a treated matter of the culture, a culture of a microorganism capable of producing pyruvic acid or

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a treated matter culture when a microorganism having NANA aldolase activity is used in the step above, or culture of a microorganism capable of producing phosphoenol pyruvic acid or a treated matter of the culture when a microorganism having NANA-synthetase activity is used in the first above step, N-acetyl mannosamine and an energy source which is necessary for the formation of pyruvic acid or PEP to be present in an aqueous medium to form and accumulate NANA in the aqueous medium and recovering NANA from the aqueous medium wherein N-acetylmannosamine (NAM) is produced by conversion of N-acetylglucosamine(NAG) to NAM using microorganism harboring DNA encoding N-acetylglucosamine 2-epimerase derived from *Synechocystis* or treated matter of such culture followed by recovery of sialic acid from the aqueous medium.

Vann(a) et al. teach that NANA synthetase catalyzes the formation of NANA as indicated by its coupling to the CMP-NeuAc synthetase reaction. The reference also teaches that the enzyme condenses Mannosamine and Phosphoenolpyruvic acid (PEP). The reference indicates that it is the first time that anyone has demonstrated an aldolase-independent sialic acid synthetase activity in *E.coli*.

Vann(b) et al. teach the purification, properties and genetic location of above enzyme in *E.coli* K1.

Maru et al. teach a simple and large-scale production of NANA from N-acetylglucosamine (NAG) and pyruvic acid using glucosamine 2-epimerase and N-acetylneuraminate lyase (also called as aldolase), both of which enzymes were isolated and cloned into *E.coli* cells. The reference also teaches the synthesis of NANA from N-acetyl-D-mannosamine (NAM) and pyruvate using aldolase. However, because of the high costs involved

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in the method wherein the NAM is used the reference suggests the conversion of low cost NAG using the 2-epimerase enzyme to NAM which can be performed in the same reaction vessel.

Thus from the reference of Maru et al. it appears that the manufacture of the sialic acid starting from NAM or NAG and pyruvate using aldolase enzyme was well known in the art. It also appears that it was well recognized in the art that the use of NAM makes the process very expensive and methods were developed in the art to cut such costs by using low cost NAG and converting it to NAM using 2-epimerase. Examiner has not given any weight to the claim that the NAG 2-epimerase used in the instant invention is derived from *Synechocystis*. This is because any epimerase from any source is encompassed in the "Synechocystis derived" epimerase used in the above claimed process.

With all the above information found in the prior art and also due to the great commercial demand for sialic acid it would have been obvious to one of ordinary skill in the art at the time this invention was made to bring together all the above information and host cells expressing the above enzymes or culture matter of host cells expressing the above enzymes and simply to put them together and isolate the sialic acid formed. It is well established in the prior art that pyruvic acid and Phosphoenol pyruvic acid are produced literally in every microorganism that undergoes TCA cycle and respiration. Therefore, introducing *E.coli* cells or *Corynebacterium* cell ---as a source of pyruvic acid---, which are well adapted for large-scale culture methods would also be obvious to one of ordinary skill in the art. As opposed to the use of aldolase, with the teachings of Vann (a) and Vann(b) in hand it would also be obvious to one of ordinary skill in the art to replace the aldolase enzyme used in the method of Maru et al. with synthetase enzyme and arrive at the same method of making sialic acid. One of ordinary skill in the art would be motivated to

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do so because of the great commercial value of sialic acid in food and pharmaceutical industry and to make the same at lower production costs. Due to the important industrial application one would be motivated to develop a method for manufacture of large amounts of sialic acid. One of ordinary skill in the art would have a reasonable expectation of success as Maru et al. demonstrate a small and a large-scale method of making sialic acid using the very same enzymes as in the instant invention and Vann et al. teach an alternate method by way of using synthetase enzyme in place of aldolase and provide the cDNA clone for the same.

Therefore, the claims 4, 6-16, 19-22 would have been *prima-facie* obvious to one of ordinary skill in the art.

In response to the previous Office action, applicants have only amended the claims and refilled the application as an RCE.

Claims 5-18, 21-22, are rejected under 35 U.S.C. 103(a) as being unpatentable over Vann(a) et al. (Glycobiology, 1997, Vol. 7(5):697-701), or Vann(b) et al. (J. Biol. Chem., 1987, Vol. 262(36):17556-62), Maru et al. (Carbohydrate Research Vol. 306:575-578) and Baker et al. (BBRC, July 1998, 248(2):250-254). Claims 5-18, 21-22 are drawn to a similar process of producing N-acetylneuraminic acid (NANA) as stated above but differing only in the fact that N-acetylmannosamine (NAM) is produced by conversion of N-acetylglucosamine(NAG) to NAM using microorganism harboring DNA encoding N-acetylglucosamine 2-epimerase or treated matter of such culture wherein said DNA is selected from the group consisting of a DNA encoding the protein with amino acid sequence SEQ ID NO:1 and DNA having a

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nucleotide sequence SEQ ID NO:2, followed by recovery of sialic acid from the aqueous medium.

The references of Vann(a) et al., Vann(b) et al. and Maru et al. have all been discussed above. The same arguments apply for this rejection as well.

Baker et al. however, identify a homolog of *Synechocystis* ORF with the accession 1652543. The reference of Baker et al. in fact annotates the non-annotated reference of Kaneko et al. (PIR database accession No.S75649, 4-25-1997 and GenEmbl accession No. D90912, 2-7-1999 which cross refers to accession No. 1652543) and teaches that the polynucleotide sequence and the encoded amino acid sequence is that of an sugar-nucleotide epimerase of *Synechocystis*.

Thus from the reference of Maru et al. it appears that the manufacture of the sialic acid starting from NAM or NAG and pyruvate using aldolase enzyme was well known in the art. It also appears that it was well recognized in the art that the use of NAM makes the process very expensive and methods were developed in the art to cut such costs by using low cost NAG and converting it to NAM using 2-epimerase. It would have been obvious to one of ordinary skill in the art to choose any epimerase that are available in the art. On that basis it would have been obvious to one of ordinary skill in the art to choose the epimerase encoded by SEQ ID NO:2 as annotated by Baker et al. to be that of *Synechocystis* epimerase. One of ordinary skill in the art would have been motivated to use the epimerase from *Synechocystis* with SEQ ID NO:1 and encoded by SEQ ID NO:2 to simply to create a difference in the method that is already well known in the art. One of ordinary skill in the art would have a reasonable expectation of success since the use of epimerase from *Synechocystis* or for that matter from any other source still leads to the formation of NANA.


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Therefore, the claims 5-18, 21-22 simply drawn to a variant method of making NANA using an epimerase with SEQ ID NO:1 encoded by SEQ ID NO:2 would have been *prima-facie* obvious to one of ordinary skill in the art.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



MANJUNATH RAO
PATENT EXAMINER

Manjunath N. Rao. Ph.D.
March 10, 2003